UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,975	04/07/2004	Daniel Santi	020547-003700US	9532

81228 7590 08/07/2008

Fox Rothschild LLP
Bristol-Myers Squibb
2000 Market Street
10th Floor
Philadelphia, PA 19103

EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
08/07/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/820,975	SANTI ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 31-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 31-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/13/2008 has been entered.

Claims 21-30 have been cancelled. Claim 1 has been amended. Claims 31-39 are new.

Claims 1-20 and 31-39 are pending and under examination.

2. All previous rejections are withdrawn in response to Applicant's amendments to the claims filed on 05/13/2008.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hodgson (PGPUB 2002/0025561).

Hodgson teaches a method of obtaining a synthetic gene by ligating three DNA segments, the method comprising: **(a)** providing three different DNA vectors each comprising a selectable marker and a different DNA insert, wherein all DNA inserts are flanked by identical type IIS restriction sites, **(b)** cleaving each DNA vector with a type IIS enzyme to generate segments with region of identity (or ligatable ends) with an adjacent segment, **(c)** simultaneously ligating the three DNA segments, and selecting the ligation product based on the presence in the vector of the selectable marker; one or more of the DNA segments could comprise the vector and the final ligation product is a complete recombinant DNA/vector, which could be made either linear or circular (i.e., the final ligation product comprises a selection marker from one of the three vectors), and **(d)** transforming cells with the final ligation product and selecting the transformants comprising the ligation product based on the presence of the selection marker above (p. 3, paragraphs 0030 and 0031, claims 1, 5, 9, and 10). It is noted that, in order to assembly the gene from the three different DNA segments, the three different segments must be assembled in the correct order, i.e., each of the end DNA segments must necessarily comprise one region of identity (ligatable end) with the internal segment; therefore, in order to be both end DNA fragments, the internal segment must necessarily comprise two regions of identity (ligatable ends). Since Hodgson teach all claim limitations, the claimed invention is anticipated by the above-cited reference.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-20 and 31-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson, in view of each Slater et al. (PGPUB 2005/0074883, of record), Gokhale et al. (Science, 1999, 284: 482485, of record), and Santi et al. (PGPUB 2004/0166567, of record).

Hodgson's teachings are applied as above for claim 1. As indicated above, Hodgson teaches that the three inserts are flanked by identical type IIS restriction sites; therefore, the first and third cleavage sites are identical, the second and fourth cleavage sites are identical, and the 5' and 3' cleavage site in the same or two different Type 3 DNA molecules are identical (claims 2, 7-10, 14, 16-19). Hodgson also teaches and that cleavage with type IIS enzymes generates three segments with region of identity (or ligatable ends) with the adjacent segment; therefore, cleavage of the second site produces a single-stranded overhang in the in the first segment which is ligatable to a single-strand overhang of an adjacent segment, cleavage of the fourth site produces a single-stranded overhang in the in the second segment which is ligatable to a single-strand overhang of an adjacent segment, while cleavage at the 5' and 3' sites in the third fragment produces 5' and 3' single-strand overhands which are ligatable to the

single-strand overhangs of two adjacent fragments (claim 14). Additionally, Hodgson teaches that one or more of the DNA segments could comprise the vector (see above), i.e., the resulting linear first and second DNA molecule comprise the DNA segments covalently associated with the vectors having the selectable markers (claim 35). Hodgson does not teach each vector comprising a selectable and counter selectable marker each vector comprising a distinct set of selectable and counter selectable markers nor do they teach polyketide synthase (PKS) (claims 2-20 and 31-39). However, at the time the invention was made, the prior art taught the use of a combination of vectors each vector having a distinct set of selectable and counter selectable markers for the accurate selection of the final recombinant product comprising the desired insert, wherein the selectable marker could be the tetracycline resistance gene and the counter selectable marker could by the ccdB or SacB gene (see Slater et al., Fig. 6-8, p. 2 and 3, paragraphs 0012 and 0013, p. 4 and 5, paragraph 0018, p. 8, paragraph 0063, p. 12, paragraph 0095, p. 15, paragraph 0124, p. 16, paragraphs 0125- 0127 and 0131, p. 18 and 19, paragraph 0159, claims 1, 4, and 27). One of skill in the art would know to use the right combination of selectable and counter-selectable markers for the selection of the desired product. One of skill in the art would have also known to use selection based on the presence of both the first and the second selectable markers when cleaving the DNA vectors such as to obtain two of the DNA segments covalently attached to the vector to ensure that both segments are present in the final ligation product. It is noted that, at the time the invention was made, such selection schemes were also taught by Santi et al. (p. 1 and 17, paragraphs 0207

and 0214). Hodgson and Slater et al. do not teach PKS (claims 11 and 12). Gokhale et al. teach recombining modules from the naturally-occurring PKSs (p. 482, column 2). Additionally, Santi et al. teach assembling synthetic PKS genes by providing different DNA vectors each comprising different selectable and counter selectable markers and different DNA inserts, wherein the DNA inserts are flanked by type IIS restriction sites, cleaving the vectors and ligating the resulting inserts to obtain the synthetic PKS genes (Abstract, p. 2 and 3, paragraphs 0019 and 0020, p. 9, paragraph 0105, p. 12 and 13, paragraphs 0154 and 0162). It would have been obvious to one of skill in the art, to use the method of Hodgson and Slater et al. to obtain synthetic PKSs as taught by Gokhale et al. and Santi et al., with a reasonable expectation of success. The motivation to do so is provided by Gokhale et al. who teach PKSs have a modular structure, and novel combinations of modules could result the synthesis of diverse medicinally important new products (Abstract, p. 482, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making such synthetic genes because Hodgson and Slater et al. teach the successful *in vitro* synthesis of genes by their method and because Santi et al. teach that synthetic PKS genes can be successfully obtained. It is noted that the instant specification defines specification Type I, II, and III vectors as vectors containing an insertion site for the DNA segment and selectable markers, wherein the only difference between the Type I, II, and III vectors is that each contains a different the selectable marker as compared to the others (see p. 19, paragraph 0230). Therefore, by using a method according to the combined teachings of Hodgson, Slater et al., and Gokhale et al. (i.e., employing different selectable and/or

counter selectable markers on each vector), one of skill in the art would use Type I, II, and III molecules.

With respect to the limitation of the presence of at least two Type 3 DNA molecules (claims 15 and 18), it is noted that the Type 3 DNA molecules contain the interior segments. One of skill in the art would know to use more than one Type 3 DNA molecule, depending on the need to add more modules to the synthetic gene, especially that Hodgson teaches his method as being suitable to be used with multiple internal segments (p. 3, paragraph 0031). With respect to claim 4, one of skill in the art would have been motivated to isolate the final ligation product from the transformants in order to sequence or transfer it to another vector, as needed; it is noted that such isolation is routine in the art. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejections.

Applicant argues that Slater is directed to directional sub-cloning of DNA fragments but is relied on by the Office for describing use of selectable markers. Applicant points out that Slater's Figure 6A and paragraph 0013 disclose a DNA insert A-B' is in a vector with a first selectable marker ("Drug 1") which is excised to produce the linear fragment A-B' and a second vector with a different selectable marker ("Drug 2") which is digested to produce linear fragment A'-B'; the first linear fragment is ligated ("directional sub-cloning") to the second linear fragment to produce a vector containing

both fragments. Therefore, paragraph 0013 does not in any way suggest the present invention; paragraph 0094, which is in the Detailed Description describes essentially the same process as described in paragraph 0013, paragraph 0063 defines the term "selectable marker", while paragraph 0125 describes types of selectable markers. Applicant submits that selectable markers have been known in the art for decades and those of skill have known for decades how to use such markers to select ligation products; however, nothing in Slater suggests or leads to Applicants' invention as claimed. Applicant reiterates that the Office has not considered the invention as claimed, but appears to consider only on a few selected individual elements in isolation. For example, the Office focuses exclusively on the fact that claimed method relies, in part, on the use of selectable markers. The Office repeatedly discounts the fact that Applicant's claim is directed to coordinated use of multiple different vectors, which involves markers, vector sequences, and combination of cleavage sites organized to accomplish the invention. Applicant submits that Examiner's statement that Type 1, 2 and 3 molecules differ only with respect to the selectable markers" (citing paragraph 0230 of the published application, US 2005/0227316) is incorrect; as has been noted before, this is not correct. Paragraph 0230 does not contain the word "only." Claim 2 itself plainly recites specific differing characteristics of the Type 1, Type 2 and Type 3 molecules. Finally, reference to paragraphs [0231]-[0235], original claims 21-26, the Figures (e.g., Figures 20A-C), and the remainder of the specification illustrates that Type I, Type 2 and Type 3 vectors have other differences, not limited to the position of the selectable marker with relation to other vector elements.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

With respect to Slater et al., it is noted that the reference was cited for the teaching of selectable and counter selectable markers and not for teaching the claimed invention. Even Applicant admits that selectable markers have been known in the art for decades and those of skill have known for decades how to use such markers to select ligation products (see Applicant's arguments above). Therefore, it is clear that, based on the teachings in the prior art, one of skill in the art would have known to use combinations of selectable and counter selectable markers to select for the desired ligation product. With respect to the Type 1, 2, and 3 DNA molecules and the disclosure in paragraph 0230, paragraph 0230 does not need to contain the word "only", since the paragraph does not disclose any other difference besides the selectable markers. Therefore, the paragraph only discloses one difference between the Type 1, 2, and 3, DNA molecules, i.e., each DNA molecule contains a different selectable marker. Claim 2 does not add to this disclosure, since the claim only requires that the inserts and the selectable markers be different between the three molecule types; there is nothing else in the claim which would distinguish one type of molecule from another or which would distinguish the three types of molecules over the combined teachings of Hodgson and Slater et al., as set forth above. While the claim does recite that the first and third cleavage sites are identical, that the second and fourth cleavage sites are identical, and that the 5' and 3' cleavage site in the Type 3 DNA molecules are identical, such limitations are taught by Hodgson (see above). Paragraphs [0231]-[0235] of the

specification disclose the prediction of the restriction sites in the gene to be constructed, clearing some restriction sites from the codon-optimized gene, and introducing new restriction sites without changing the encoded amino acid sequence. Such disclosure is related to the inserts and does not support Applicant's assertion that Type 1, 2, and 3 molecules differ by more than selection markers. Original claims 21-26, the Figures 20A-C), and paragraph 0182 of the instant specification disclose that Type 1, 2, and 3 molecules all contain the same insertion site for the DNA fragment, the same selectable and counter selectable markers (Type 1 and 2 could comprise additionally unique selectable markers); the type IIS restriction sites are the same for all three molecule types. Therefore, the specification defines that Type 1, 2, and 3 molecules only differ with respect to selectable markers. As indicated above, and as admitted by Applicant, selectable markers have been known in the art for decades and those of skill have known for decades how to use such markers to select ligation products. Therefore, the instant method is rendered obvious by the teachings of the prior art cited above and the rejection is maintained.

7. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD
/Ileana Popa/
Art Unit 1633